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# (12) EUROPEAN PATENT APPLICATION

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## (54) Synthesis of 2-deoxy-2-fluoro-arabinose derivates

(57) A process for deoxofluorinating a $C_2$-hydroxyl group of a furanose, includes: (a) mixing the furanose and a deoxofluorinating agent in a solvent to form a reaction mixture, and (b) heating the reaction mixture to greater than about 50°C. The process provides deoxofluorinated products, such as 2-fluoroarabinoses, in yields of at least 80% of theoretical.

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yethyl)aminosulfur trifluorides provide more thermally stable fluorine-bearing compounds which have effective fluorinating capability with far less potential of violent decomposition and attendant high gaseous byproduct evolvement, with simpler and more efficient fluorinations. Furthermore, bis(2-methoxyethyl)aminosulfur trifluorides can efficiently effect the transformation of hydroxy and carbonyl functionalities to the corresponding fluoride and *gem*-difluoride respectively.

**[0009]** It has been observed that the direct replacement of a leaving group at the 2'-position of a pyrimidine nucleoside by the fluoride ion is complicated by neighboring-group participation of the carbonyl group of the base, resulting in the formation of the anhydronucleoside. See Fox, 18 J. Pure Appl. Chem. 223 (1969). In the synthesis of 2'-fluoropurines, attempts to replace a $C_2$ protecting group (e.g., triflate) with fluoride resulted in base cleavage and formation of olefinic byproducts. See Pankiewicz et al., 64 J. Fl. Chem. 15 (1993). It has also been observed that the direct deoxofluorination of the 2'-hydroxyl of some purine derivatives by diethylaminosulfur trifluoride (DAST) afford only low yields of products even when a large excess of the fluorinating agent is used. See Pankiewicz et al., 57 J. Org. Chem. 553 (1992).

**[0010]** The synthesis of 2'-fluoro-substituted nucleosides is currently carried out by condensation of the appropriate 2-fluoro sugar derivative with the nucleoside base. See Pankiewicz et al., 15 J. Fl. Chem. 64 (1993). However, the fluoro sugar is not easily accessible since its preparation often involves lengthy multistep and low yielding procedures. See Reichmann et al., 42 J. Cardohydr. Res. 233 (1975). The nucleophilic displacement of a leaving group by fluoride at C-2 of furanosides is often accompanied by elimination reactions resulting in olefinic byproducts. See Tann et al., 50 J. Org. Chem. 3644 (1985). Tann et al. reported on a three-step synthesis of 2-deoxy-2-fluoro-1,3,5-tri-O-benzoyl-α-D-arabinofuranose via a 2-O-imidazolylsulfonate leaving group using $KHF_2$ as the source of fluoride. Tann et al. found that the direct replacement of the $C_2$-hydroxyl of this sugar by F with diethylaminosulfur trifluoride (DAST) failed.

**[0011]** Despite the findings in Tann et al., it has been shown that DAST has been used successfully for the deoxofluorination of hydroxy groups of six-membered ring sugars and the $C_3$ hydroxyl of five-membered ring sugars (i.e., furanoses). See Welch et al., *Fluorine in Bioorganic Chemistry*, p. 131 (John Wiley and Sons, 1991). Additionally, the procedure of Tann et al. was improved upon by Chou et al. (37 Tett. Lett. 1 (1996)) where triethylamine poly(hydrogen fluoride) was used as the source of fluoride.

**[0012]** Accordingly, there remains a need in the art for a process effective to deoxofluorinate the $C_2$-hydroxyl group of furanoses.

**[0013]** All references cited herein are incorporated herein by reference in their entireties.

## BRIEF SUMMARY OF THE INVENTION

**[0014]** The invention provides a process for deoxofluorinating a $C_2$-hydroxyl group of a furanose. The process comprises mixing the furanose and a deoxofluorinating agent in a solvent to form a reaction mixture, and heating the reaction mixture to greater than about 50°C.

**[0015]** Also provided are products produced by the process of the invention.

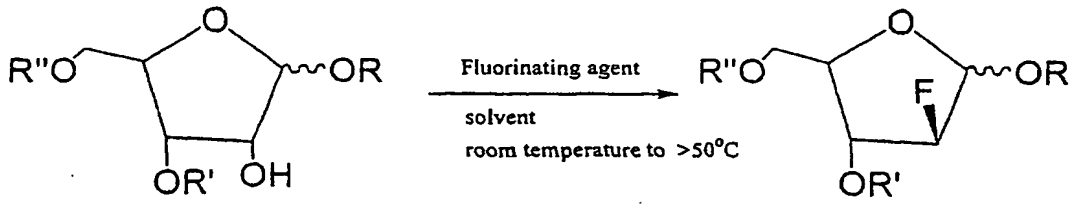
## BRIEF DESCRIPTION OF SEVERAL VIEWS OF THE DRAWINGS

**[0016]** Not applicable.

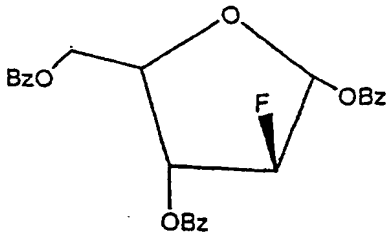
## DETAILED DESCRIPTION OF THE INVENTION

**[0017]** A preferred process of the invention comprises deoxyfluorinating a hydroxylated ring carbon of a sugar with a fluorinating agent in the presence of a solvent. A preferred embodiment of the invention is shown in Equation I:

Equation I



Formula I




Bz = COPh

**[0029]** The NMR spectral characteristics obtained were $^1$H NMR ($CDCl_3$) d 8.2-7.95 (m, 6H), 7.75- 7.5 (m, 3H), 7.5 - 7.35 (m, 6 H), 6.75 (d, 1H, J = 9 Hz), 5.65 (dd, 1H, J = 18 Hz, 3 Hz), 5.35 (d, 1H, J = 48 Hz), 4.85-4.75 (m, 1H), 4.75-4.65 (m, 2H). $^{19}$F NMR ($CDCl_3$) d - 191.

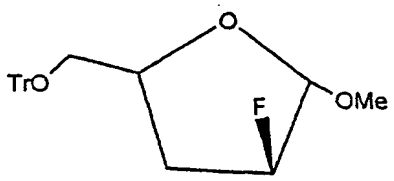
Example 2: Fluorination of 1,3,5-tribenzoyl-α-D-ribofuranose with DAST

**[0030]** Deoxofluorination was performed as in Example 1, with DAST (80 mg, 0.5 mL) substituted for bis(2-methoxyethyl)aminosulfur trifluoride. The reaction yielded 217 mg (96% yield) of 2-deoxy-2-fluoro-1,3,5-tri-O-benzoyl-α-D-arabinofuranose (Formula I, above). The NMR spectral characteristics were the same as in Example 1.

Example 3: Fluorination of 3-deoxy-1-methoxy-5-trityl-α-D-ribofuranoside with Bis(2-methoxyethyl)aminosulfur trifluoride

**[0031]** Deoxofluorination of 3-deoxy-1-methoxy-5-trityl-α-D-ribofuranoside (388 mg, 1 mmol) was performed as in Example 1, using 243 mg (1.1 mmol) of bis(2-methoxyethyl)aminosulfur trifluoride in 5 mL of toluene. The reaction yielded 324 mg (83% yield) of 3-deoxy-2-fluoro-1-methoxy-5-trityl-α-D-arabinofuranose (Formula II, below) as a mixture of anomers.

Formula II




Tr = $C(Ph)_3$

**[0032]** The NMR ($^1$H NMR ($CDCl_3$)) spectral characteristics obtained were: (major anomer) d 7.5-7.3 (m, 4.5 H), 7.3-7.1 (m, 4.5 H), 7.1-7.0 (m, 2.25 H), 5.0 (d, 0.75 H), 4.8 (dm, 0.75 H), 4.35-4.10 (m, 0.75), 3.3-3.0 (m, 1.5 H), 3.3 (s, 2.25H), 2.4-2.1 (m, 0.75H), 1.9-1.7 (m, 0.75 H). $^{19}$F NMR d -180. $^1$H NMR ($CDCl_3$) (minor anomer), d d 7.5-7.3 (m, 1.5 H), 7.3-7.1 (m, 1.5 H), 7.1-7.0 (m, 0.75 H), 5.0 (d, 0.25 H), 4.9 (dm,0.25 H), 4.35-4.10 (m, 0.25 H), 3.7-3.5 (m, 0.5H), 3.3 (s, 0.75H), 1.8-1.3 (m, 0.5H). $^{19}$F NMR ($CDCl_3$) -180.

quenching said deoxofluorinating in said heated reaction mixture to provide a quenched mixture; and purifying a deoxofluorinated product from said quenched mixture.

**9.** The process of claim 1, further comprising:

quenching said deoxofluorinating in said heated reaction mixture to provide a quenched mixture; and isolating a deoxofluorinated product from said quenched mixture.

**10.** The process of claim 9, wherein a yield of said deoxofluorinated product is at least 80% of theoretical.

**11.** The process of claim 10, wherein said yield is at least 95%.

**12.** The process of claim 1, wherein said deoxofluorinating agent is an aminosulfur trifluoride.

**13.** The process of claim 12, wherein said deoxofluorinating agent is at least one member selected from the group consisting of diethylaminosulfur trifluoride, bis(2-methoxyethyl) aminosulfur trifluoride, perfluorobutanesulfonyl fluoride, 2-chloro-1,2,3-trifluoroethyldiethylamine and hexafluoroisopropyl diethylamine.

**14.** The process of claim 13, wherein said deoxofluorinating agent is bis(2-methoxyethyl) aminosulfur trifluoride.

**15.** The process of claim 1, wherein said solvent is non-polar.

**16.** The process of claim 1, wherein said solvent is at least one member selected from the group consisting of halocarbons, hydrocarbons, ethers, amides and esters.

**17.** The process of claim 1, wherein said solvent is toluene.

**18.** The process of claim 1, further comprising substituting a protecting group for each hydroxyl group of said furanose other than said $C_2$-hydroxyl group.

**19.** The process of claim 18, wherein said protecting group is at least one member selected from the group consisting of esters, ethers, sulfonates, acetals and orthoesters.

**20.** The process of claim 18, wherein said protecting group is at least one member selected from the group consisting of benzoyl, trityl or triflate.

**21.** The process of claim 18, wherein said furanose an arabinofuranose.

**22.** The process of claim 18, wherein said furanose is a ribofuranose.

**23.** The process of claim 22, wherein said furanose is 1,3,5-tribenzoyl-α-D-ribofuranose, 1,3,5-tribenzoyl-α-L-ribofuranose or 3-deoxy-1-methoxy-5-trityl-α-D-ribofuranose.

**24.** The process of claim 22, wherein a product of said deoxofluorinating is a 2-deoxy-2-fluoro-arabinofuranose.

**25.** The process of claim 24, further comprising replacing a $C_1$ hydroxyl group with a pyrimidine or a purine.

**26.** A 2-deoxy-2-fluoro-arabinofuranose produced by the process of claim 24.

**27.** A 2'-deoxy-2'-fluoro-arabinofuranoside produced by the process of claim 25.

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**INCOMPLETE SEARCH**
**SHEET C**

Application Number
EP 01 11 5797

Claim(s) searched completely:
1-25

Claim(s) searched incompletely:
26,27

Reason for the limitation of the search:

Claims 1-25 have been searched completely. As for claims 26 and 27, the initial phase of the search revealed a very large number of documents relevant to the issue of novelty of the claimed compounds per-se. So many documents were retrieved that it is impossible to determine which parts of claims 26 and 27 may be said to define subject-matter for which protection might legitimately be sought (Article 84 EPC). For these reasons, a meaningful search over the whole breadth of claims 26 and 27 is impossible. Consequently, the search can only be considered complete for claims 1-25, and for the examples given for the subject-matter of claims 26 and 27.

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# PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 01 11 5797

| DOCUMENTS CONSIDERED TO BE RELEVANT | | | CLASSIFICATION OF THE APPLICATION (Int.Cl.7) |
|---|---|---|---|
| Category | Citation of document with indication, where appropriate, of relevant passages | Relevant to claim | |
| X | WO 96 06103 A (SAISCHEK JOERN ;STADELMANN BERNDT (US)) 29 February 1996 (1996-02-29) * pages 14 - 18, examples 5, 6, 9, 13-15 * | 26,27 | |
| X | PANKIEWICZ: "FLUORINATED NUCLEOSIDES" CARBOHYDRATE RESEARCH, vol. 327, 10 July 2000 (2000-07-10), pages 87-105, XP004215278 * page 88, FMAU; page 89, cpd. 6, F-ara-A, F-ara-C; page 90, IDUVIRAN, FIAC, FEAU, cpds.11,12,14,15; page 91, cpds. 17,20,26,27,32, C-FMAU,33; page 94, F-ara-ddA; page 95, L-FMAU * | 26,27 | |
| X | MARUYAMA ET AL.: "SYNTHESIS AND ANTIVIRAL ACTIVITY OF 6-CHLOROPURINE ARABINOSIDE AND ITS 2'-DEOXY-2'-FLUORO DERIVATIVE" CHEMICAL AND PHARMACEUTICAL BULLETIN, vol. 44, no. 12, 1996, pages 2331-2334, XP002177626 * page 2331, scheme, compounds 3b, 4, 7 * | 27 | TECHNICAL FIELDS SEARCHED (Int.Cl.7) |
| X | MARUYAMA ET AL.: "SYNTHESIS OF 9-(2-DEOXY-2-FLUORO-BETA-D-ARABINOFURANOSYL)ADENINE BEARING A SELECTIVELY REMOVABLE PROTECTING GROUP" CHEMICAL AND PHARMACEUTICAL BULLETIN, vol. 47, no. 7, 1999, pages 966-970, XP002177627 * page 967, scheme, compounds 1, 2, 6-9 * | 27 | |

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